REMARKS

In view of the above amendments and the following remarks, reconsideration of this application is respectfully requested.

Status of the Claims

Upon entry of the amendments presented herein, claims 32-41, 43, 46, and 49-52 will be pending. Claims 32-37, 39-41, 43, 46, and 49-52 are hereby amended. Claims 42, 44, 45, 47, 48, and 53 are hereby canceled without prejudice. Claims 1-31 were previously canceled without prejudice. No new matter has been added by way of the claim amendments presented herein.

Rejection Under 35 U.S.C. § 112, 1st Paragraph

Claims 32-53 are rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the written description requirement.

With regard to claims 42, 44, 45, 47, 48, and 53, this rejection is rendered moot in view of the cancellation of those claims.

Regarding claims 32-41, 43, 44, 46, and 49-52, this rejection is respectfully traversed in view of the above amendments to the claims and the following remarks.

To support this rejection, the Examiner has asserted that the specification does not define the term "derivative" as recited in the rejected claims (*see* Office Action, at page 2). However, the Examiner has acknowledged that the specification does describe a "salt" of the amino acids recited in the claims (*see* Office Action, at page 3).

The claims have been amended to replace the term "derivative" (or variations thereof) with the term "salt" (or variations thereof). Applicant respectfully submits that these claim amendments are sufficient to overcome the written description rejection.

For the foregoing reasons, applicant respectfully submits that the rejection of claims 32-53 for alleged lack of written descriptive support is improper and should be withdrawn.

Rejections Under 35 U.S.C. § 112, 2nd Paragraph

Claims 32-53 are rejected under 35 U.S.C. § 112, second paragraph, for indefiniteness for allegedly failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In view of the above amendments and the following remarks, applicants respectfully traverse this rejection.

The Examiner has taken the position that the metes and bounds of the claims of the present invention are not defined in the claims or specification, because neither define how much an amino acid may be modified, substituted, or otherwise altered while still being considered a derivative of the recited amino acid (*see* Office Action, at page 4).

As stated in rebuttal of the preceding written description rejection, the claims have been amended to replace the term "derivative" (or variations thereof) with the term "salt" (or derivatives thereof). This amendment is sufficient to obviate the present rejection for indefiniteness.

Therefore, applicant respectfully submits that this rejection is improper and should be withdrawn.

Claims 39-42, 52, and 53 are rejected under 35 U.S.C. § 112, second paragraph, for indefiniteness for allegedly failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner has taken the position that the phrase "envisaged in the composition" as recited in the rejected claims is indefinite. This phrase has been deleted from the claims.

In view of the foregoing, applicant respectfully submits that this rejection is improper and should be withdrawn.

Rejections Under 35 U.S.C. § 102(b)

In order to support a rejection based on anticipation, the cited prior art reference must teach each and every element of the rejected claim. As set forth below, it is clear that Volpi fails to meet this standard. Therefore, with respect to each of the rejections for anticipation (based on 35 U.S.C. § 102), applicant respectfully submits that this rejection is improper and should be withdrawn.

Volpi

Claims 32, 35, and 43-48 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Volpi et al., "Exogenous Amino Acids Stimulate Net Muscle Protein Synthesis in the Elderly," *J. Clin. Invest.* 101(9):2000-2007 (1998) ("Volpi").

In view of the above amendments and the following remarks, applicants respectfully traverse this rejection.

In support of this rejection, the Examiner gave no weight to the claim limitations that: (i) the method of claim 32 relates to maintaining intact, restoring, and/or increasing the number of cellular mitochondria in an elderly subject, and (ii) the method of claim 43 relates to the treatment of apoptosis of mitochondrial origin in a subject. While applicant asserts that these limitations render the rejected claims distinguishable over the cited art, applicant has further amended the claims to introduce claim limitations that are clearly not found in the cited art, as discussed in detail below.

Independent claims 32 and 43 have been amended to recite that the therapeutically effective amount of the composition of the present invention is "chronically administering via oral route" (emphasis indicates inserted text in the amended claims). Support for these amendments are found in the specification at least at page 11, lines 21-24, and page12, lines 16-21.

Unlike the claims of the present invention, Volpi relates to an intravenous infusion of amino acid mixtures. The experimental procedure in Volpi involved starting a primed, continuous infusion of phenylalanine, followed after 60 minutes by leucine, lysine and alanine (*see* Volpi, at page 2001, left column); this tracer infusion was maintained until the end of the experiment. After the basal period (0-300 min), a further primed, continuous infusion of

"10% Travasol" was started (*see* Volpi, at page 2001, right column). The two infusions were then maintained until the end of the experiment (480 min) (*Id.*).

Details concerning 10% Travasol, i.e., a composition for injection, are available at the following Internet address: www.drugs.com/pro/travasol.html. In particular, 10% Travasol includes amino acids alanine, arginine, glycine, proline and serine, which amino acids are not included in the composition according to the present invention.

The investigation of Volpi is aimed at demonstrating that amino acids alone can stimulate muscle protein anabolism and synthesis in elderly individuals. The study shows that intravenous infusion of the Travasol amino acid mixture significantly increased amino acid delivery to the leg, amino acid transport, and muscle protein synthesis. Protein breakdown did not change during amino acid infusions, such that a positive net balance of amino acids across the muscle was achieved. The authors of Volpi thus concluded that, although muscle mass is decreased in the elderly, muscle protein anabolism can nonetheless be stimulated by increased amino acid availability. Therefore, the authors of Volpi hypothesize that muscle mass could be better maintained with an increased intake of protein or amino acids.

Unlike in Volpi, the composition according to the present invention is administered chronically and by an oral route. This method of administration is different and unquestionably entails different effect from an infusion, as devised in Volpi. Further, it is clear that the therapeutic purposes of Volpi and the present invention are different.

In addition, the present application shows that perfusion of the amino acids mixture according to the present invention gives no significant effects compared to chronic administration by oral route (*see, e.g.,* the Specification, at page 10, line 15 to page 11, line 24).

Furthermore, the composition used in the experiment of Volpi (i.e., 10% Travasol) does not meet the limitations of the outstanding claims.

In view of the foregoing, applicant respectfully submits that the rejection of the claims for anticipation based on Volpi is improper and should be withdrawn.

Ozeki

Claims 43-51 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by U.S. Patent No. 5,036,052 to Ozeki et al. ("Ozeki"). In view of the above amendments and the following remarks, applicant respectfully traverses this rejection.

In setting forth this rejection, the Examiner gave no weight to the limitation of the method of claim 43 that relates to the treatment of apoptosis of mitochondrial origin in a subject. While applicant asserts that this limitation renders the rejected claims distinguishable over the cited art, applicant has further amended the claims to introduce claim limitations that are clearly not found in the cited art, as discussed in detail below.

Ozeki specifically refers to amino acid infusion solutions for intravenous administration. In particular, Ozeki aims to achieve the following:

(i) provide stable, L-amino acid-containing nutrient aqueous compositions that contain Tryptophan in a desirable amount, but no stabilizers such as hydrogensulfites or sulfites conventionally used;

(ii) present an amino acid nutrient infusion composition of a new formulation that contains sparingly soluble tyrosine in an amount necessary at a ratio achieving the purpose without being subject to the pharmaceutical restrictions, and that can exert an excellent nutrient effect to the various intended diseases;

(iii) provide L-amino acid compositions for infusion in which a rate of the branched chain amino acid components is increased; and

(iv) provide branched chain amino acid compositions which are used for preparing amino acid infusion solutions that are free from any preparation restrictions but contain BCAA in a large ratio suited for the purpose in a necessary dose by simply adding such BCAA composition to an ordinary amino acid infusion solution when administered.

In order to attain the above aims, Ozeki proposes an infusion composition (that contains almost all known amino acids) in which at least one of some specific L-amino acids is contained partly or substantially completely in the form of oligopeptides containing at least one residue of the same L-amino acid.

Thus, as with Volpi, the composition of Ozeki is specifically provided for intravenous administration, which is clearly distinguishable and entails different therapeutic effects compared to the chronic oral administration according to the present invention. As already mentioned above, the present application shows that perfusion gives different effects with respect to chronic administration by oral route.

Additionally, it is noted that peptides, as devised by Ozeki, cannot be administered orally for therapeutic purposes, since they are digested. If digested, a peptide loses any therapeutic function.

It is finally noted that the intravenous compositions of Ozeki do not meet the limitations of the pending claims.

In view of the foregoing, applicant respectfully submits that the rejection of the claims for anticipation based on Ozeki is improper and should be withdrawn.

Dioguardi '420

Claims 32, 35, 38, and 43-49 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by U.S. Patent No. 6,218,420 to Dioguardi ("Dioguardi '420"). In view of the above amendments and the following remarks, applicant respectfully traverses this rejection.

The Examiner has given no weight to the limitations that (i) the method of claim 32 relates to maintaining intact, restoring, and/or increasing the number of cellular mitochondria in an elderly subject, and (ii) the method of claim 43 relates to the treatment of apoptosis of mitochondrial origin in a subject. While applicant asserts that this limitation renders the rejected claims distinguishable over the cited art, applicant has further amended the claims to introduce claim limitations that are clearly not found in the cited art, as discussed in detail below.

In particular, independent claims 32 and 43 have been amended to import the molar ratio limitations of now canceled claims 42 and 53, respectively.

Unlike the claims of the present invention, Dioguardi '420 relates to a composition and a method for generally regulating nitrogen in a body. While Dioguardi '420 teaches using a composition including the same amino acids as in the instant invention and which can be administered orally, it does not give any specific molar ratios among the amino acids. Instead, Dioguardi '420 only stipulates that the individual amounts of threonine and lysine

are greater than the individual amounts of histidine, methionine, phenylalanine, and tryptophan (i.e., the essential amino acids).

Further, the composition of Dioguardi '420 does not meet the limitations of the pending claims.

In view of the foregoing, applicant respectfully submits that the rejection of the claims for anticipation based on Dioguardi '420 is improper and should be withdrawn.

Rejections Under 35 U.S.C. § 102(e)

Conti '756

Claims 43-49 are rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by U.S. Patent Application Publication No. US-2004/0192756 to Conti et al. ("Conti '756"). In view of the above amendments and the following remarks, applicant respectfully traverses this rejection.

The Examiner has given no weight to the limitation that the method of claim 43 relates to the treatment of apoptosis of mitochondrial origin in a subject. While applicant asserts that this limitation renders the rejected claims distinguishable over the cited art, applicant has further amended the claims to introduce claim limitations that are clearly not found in the cited art, as discussed in detail below.

Unlike the claims of the present invention, Conti '756 relates to a composition for use in the ophthalmic field for the healing and/or mending of wounds and lesions, which is completely different from the instant invention.

Conti '756 discloses a composition that includes the same amino acids as in the present invention and that can be administered orally. However, the composition of Conti '756 also includes very high amounts of proline and glycine, which are amino acids required for promoting collagen synthesis, and which have no effect in the frame of the instant invention. Rather, they can be counterproductive, since they are useless for mitochondria proliferation. In particular, these unnecessary additional amino acids must be eliminated by tissues, and may possibly become a risky burden for local metabolism.

Further, the composition of Conti '756 does not meet the limitations of the pending claims.

In view of the foregoing, applicant respectfully submits that the rejection of the claims for anticipation based on Conti '756 is improper and should be withdrawn.

Conti '903

Claims 43-49 are rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by U.S. Patent Application Publication No. US-2004/0157903 to Conti et al. ("Conti '903"). In view of the above amendments and the following remarks, applicant respectfully traverses this rejection.

To support this rejection, no weight was given to the limitation that the method of claim 43 relates to the treatment of apoptosis of mitochondrial origin in a subject. While applicant asserts that this limitation renders the rejected claims distinguishable over the cited art, applicant has further amended the claims to introduce claim limitations that are clearly not found in the cited art, as discussed in detail below.

Unlike the present invention, Conti '903 relates to a composition for improving the myocardial ventricular function in diabetic patients, which is completely different from the instant invention.

Further, although Conti '903 discloses a composition that includes some of the same amino acids as in the instant invention and that can be administered orally, the composition of Conti '903 does not meet the limitations of the present claims.

In view of the foregoing, applicant respectfully submits that the rejection of the claims for anticipation based on Conti '756 is improper and should be withdrawn.

Rejections Under 35 U.S.C. § 103(a)

For an obviousness rejection to be proper, the Examiner must meet the burden of establishing that all elements of the invention are disclosed in the prior art; and must show that the prior art relied upon, or knowledge generally available in the art at the time of the invention, provides some suggestion or incentive that would have motivated the skilled artisan to modify a reference or combine references. *In re Fine*, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988).

"A patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007). To find obviousness, the Examiner must "identify a reason that would have prompted a person of ordinary skill in the art in the relevant field to combine the elements in the way the claimed new invention does." *Id.* Therefore, in issuing an obviousness rejection, the Examiner must not simply engage in a hindsight analysis based on the disclosure of the application at issue.

In view of the above amendments and the following remarks, the Examiner has failed even to meet a *prima facie* case of obviousness. Thus, applicant respectfully submits that the rejections based on obviousness are improper and should be withdrawn.

Volpi and Ozeki

Claims 33, 34, 36-42, 52, and 53 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Volpi in view of Ozeki. In view of the above amendments and the following remarks, applicants respectfully traverse this rejection.

The Examiner states that it would have been obvious to optimize concentrations, amounts, and/or ratios of amino acids in the compositions of the cited references through routine tests, in view of attaining the subject matter of the instant claims. Applicant respectfully disagrees.

The deficiencies of Volpi and Ozeki have been set forth above in rebuttal of their use in supporting anticipation rejections against the claims. The Examiner has not provided any further reasonable grounds to support an obviousness rejection based on Volpi and Ozeki. In essence, the Examiner's rationale for this rejection lies in the improper conclusion that, if a composition for a certain therapeutic use were known, including all known amino acids, then

there would be no possibility to obtain patents for other compositions directed to other therapeutic uses, because the prior composition would be capable in any case of performing all possible intended uses (even the undisclosed ones), and that the ordinarily skilled man could easily adjust proportions depending upon the desired use.

The Examiner's rationale in support of this rejection is completely at odds with the scientific realities relating to methods for treating apoptosis in a subject (*see* claim 43) or for maintaining intact, restoring, and/or increasing the number of cellular mitochondria in an elderly subject (*see* claim 32). One cannot simply add and subject amino acids or other seemingly therapeutic constituents and expect to have a treatment for a particular condition of a subject. Instead, careful experimentation is required. Such experimentation is anything but routine. Thus, absent undue and lengthy experimentation, one of ordinary skill would not reasonable arrive at the methods of the present invention by combining Volpi and Ozeki.

Further, as mentioned above, it is not seen why one skilled in the art would be motivated to perform routine tests to attain the instant invention, based on documents that relate to different therapeutic treatment and ways of administration.

In view of the foregoing, applicant respectfully submits that the rejection of the claims for obviousness over Volpi in view of Ozeki is improper and should be withdrawn.

Dioguardi '420

Claims 33, 34, 36, 37, 39-42, and 50-53 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Dioguardi '420. In view of the above amendments and the following remarks, applicant respectfully traverses this rejection.

The deficiencies of Dioguardi '420 are set forth above. The Examiner provides no further arguments that can reasonably be interpreted as rendering the claims of the present invention, as amended, obvious.

In view of the foregoing, applicant respectfully submits that the rejection of the claims for obviousness over Dioguardi is improper and should be withdrawn.

Conti '756

Claims 50-53 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Conti '756. In view of the above amendments and the following remarks, applicant respectfully traverses this rejection.

The deficiencies of Conti '756 are set forth above. The Examiner provides no further arguments that can reasonably be interpreted as rendering the claims of the present invention, as amended, obvious.

In view of the foregoing, applicant respectfully submits that the rejection of the claims for obviousness over Conti '756 is improper and should be withdrawn.

Conti '903

Claims 50-53 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Conti '903. In view of the above amendments and the following remarks, applicant respectfully traverses this rejection.

The deficiencies of Conti '903 are set forth above. The Examiner provides no further arguments that can reasonably be interpreted as rendering the claims of the present invention, as amended, obvious.

In view of the foregoing, applicant respectfully submits that the rejection of the claims for obviousness over Conti '903 is improper and should be withdrawn.

Rejections for Nonstatutory Obviousness-Type Double Patenting

Dioguardi '420

Claims 43-53 are rejected for nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 8 and 9 of Dioguardi '420. In view of the above amendments and the following remarks, applicant respectfully traverses this rejection.

The deficiencies of Dioguardi '420 are set forth above. The Examiner provides no further arguments that can reasonably be interpreted as rendering the claims of the present invention, as amended, obvious over claims 8 and 9 of Dioguardi '420 on nonstatutory obviousness-type double patenting grounds.

In view of the foregoing, applicant respectfully submits that this rejection based on Dioguardi '420 is improper and should be withdrawn.

Conti '141 Application

Claims 43-53 are *provisionally* rejected for nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 35-39 of co-pending U.S. Patent Application Serial No. 10/486,141 to Conti et al. ("Conti '141 application"), which corresponds to Conti '756. In view of the above amendments and the following remarks, applicant respectfully traverses this rejection.

The deficiencies of the Conti '141 application (i.e., Conti '756) are set forth above. The Examiner provides no further arguments that can reasonably be interpreted as rendering the claims of the present invention, as amended, obvious over claims 35-39 of the Conti '141 application on nonstatutory obviousness-type double patenting grounds.

In view of the foregoing, applicant respectfully submits that this rejection based on the Conti '141 application is improper and should be withdrawn.

Dioguardi '236 Application

Claims 43-53 are *provisionally* rejected for nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 33-54 of co-pending U.S. Patent Application Serial No. 10/332,236 to Dioguardi ("Dioguardi '236 application"). In view of the above amendments and the following remarks, applicant respectfully traverses this rejection.

Applicant asserts that, as amended, the claims of the present invention cannot be viewed as being obvious over claims 33-54 of the Dioguardi '236 application. This is readily apparent from a comparison of the now pending claims in the Dioguardi '236 application and those of the present invention.

In view of the foregoing, applicant respectfully submits that this rejection based on the Dioguardi '236 application is improper and should be withdrawn.

Conti '722 Application

Claims 43-53 are *provisionally* rejected for nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 16-35 of co-pending U.S. Patent Application Serial No. 12/104,722 to Conti et al. ("Conti '722 application"). In view of the above amendments and the following remarks, applicant respectfully traverses this rejection.

Applicant asserts that, as amended, the claims of the present invention cannot be viewed as being obvious over claims 16-35 of the Conti '722 application. This is readily apparent from a comparison of the now pending claims in the Conti '722 application and those of the present invention.

In view of the foregoing, applicant respectfully submits that this rejection based on the Conti '722 application is improper and should be withdrawn.

CONCLUSION

Claims 32-41, 43, 46, and 49-52 are now under consideration in this case. In view of the all of the foregoing, applicant respectfully submits that the claims of the present application are in condition for allowance and such allowance is earnestly solicited.

If any unresolved issues remain that might prevent the prompt allowance of the present application, the Examiner is respectfully encouraged to contact the undersigned at the telephone number listed below to discuss these issues.

Submitted herewith via EFS-Web is payment in the amount of $130 for a one-month extension of time under 37 C.F.R. § 1.17(a)(1) (Large Entity). The Commissioner is hereby authorized to charge any fees that may have been overlooked, or to credit any overpayments of fees, to Deposit Account No. 08-1935.

Respectfully submitted,

HESLIN ROTHENBERG FARLEY & MESITI P.C.

By: **/Andrew K. Gonsalves/**

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